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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/033,491	ZHANG ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-78 and 80-226* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-78 and 80-226* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/12/07 has been entered.

Claims 70-78 and 80-226 are resubmitted as they were present at the time of final rejection on 8/8/06.

Claims 70-78 and 80-226 are presently pending and considered.

Note, Art Rejections:

All previous rejections under 35 USC 103(a) are withdrawn. The Examiner feels that such rejections are still proper, even in light of Applicant's arguments are excessively large IDS filing which contains no specific direction as to why such documents are relevant; however, this filing makes it apparent to the Examiner that Applicant intends to appeal the rejections under 35 USC 103(a). Because of this, the Examiner has opted to reapply the rejections with more art to support to the Examiner's rejections, and to help crystallize the issues for a possible appeal, as well as to help to Applicant understand the Examiner's logic.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-78 and 80-226 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31, and 33-37 of copending Application No. 09/203,078, for reasons of record.

Double-Patenting over 09/203,078 held in Abeyance

In accord with Applicant's request, the provisional double-patenting rejection over U.S. Application No. 09/203,078 is maintained, but remain held in abeyance (Applicant's response of 6/12/06, p. 30).

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 78, 109, 140, 171, and 202 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims encompass the limitation that the adenoviral composition be "essentially free of BSA". The specification's implicit support for such limitation on page 72, paragraph 2, where it says that the compositions should be essentially free of pyrogens as well as other impurities that could be harmful to humans or animals. However, such does not equate to the scope Applicant claims, and the Examiner has only found implicit support for such limitation, in the form of a specific method which produces BSA levels below the detection limit of a western blot assay (EXAMPLE 6), hence, outside of the specific embodiment of making the virus in EXAMPLE 6, Applicant has no support for the wide breadth claimed.

Response to Argument – New Matter

Applicant's response of 6/12/07 has been fully considered but is not found persuasive.

Applicant argues that the implicit support of EXAMPLE 6 provides adequate support for the claims, as the support may be implicit or explicit (p. 22, paragraph 4).

Such is not persuasive. The finding in EXAMPLE 6 is a result reported, and is not even recognized in such example as being the invention. Still further, an implicit support may be support for the claims, but only if commensurate with the claims. However, these claims are broader than the method of EXAMPLE 6, and they are not restricted to the steps and materials of the EXAMPLES. Hence, such implicit support fails to provide adequate support for the broad claims provided.

Applicant argues that the specification provides support for the desire to remove abnormally structured proteins (prions) by removing serum proteins (pp. 22-23, paragraph

bridging, citing p. 28, lines 11-17), that in order to accomplish this the specification teaches serum free media (p. 23, paragraph 2, citing page 7, lines 5-9), and that the pharmaceutical formulations will entail preparing a pharmaceutical composition "essentially free of pyrogens, as well as any other impurities that could be harmful to humans or animals" (p. 23, paragraph 2, citing page 72, lines 15-17).

Such is not persuasive. The specification appears to be recognizing that prions are the pyrogens which are desired to be removed, and a general acknowledgment that impurities that are harmful are desired to be removed, but does not recognize that, singularly, BSA is a pyrogen itself that is desired to be removed. And hence, at best, the support is one of obviousness, however, obviousness does not supplant the need for specific demonstration of possession. There are no blaze marks here that the Artisan could follow to find the invention to include compositions "essentially free of BSA".

Applicant argues, citing several results in the specifications EXAMPLE 6, that BSA is shown to be a principle goal of the inventors, and hence, such supports the breadth of "essentially free of BSA" (p. 23, paragraph 3).

Such is not persuasive. The various results appear to the Examiner to indicate the general indication that the methods yield compositions with generally less impurities, not that a goal of the methods is to achieve compositions "essentially free of BSA".

Applicant summarizes their arguments, stating the specification to indicate that bovine proteins constitute dangerous contaminants, the instruction that the formulations should be essentially free of pyrogens and other impurities, and the demonstration that BSA could not be

detected in a purified composition, to indicate that they possess "essentially free of BSA" (pp. 23-24, paragraph bridging).

Such is not persuasive. The confluence of the evidence taken together, as presented in the context of the specification, indicates that the invention included the aspects of removing all dangerous impurities, and specifically spongiform viruses, as indicated on p. 28, lines 11-17 and p. 72, paragraph 2, and the Artisan would consider the Examples to indicate the general purity of the virus compositions, and not specifically that the compositions should be "essentially free of BSA".

NOTE: The obviousness rejections have been reorganized in a new manner, applying rejections in various manners, and all using the same core art. These rejections are organized under sections entitled according to their key aspects, in order to allow for organized argument that is, hopefully, more easily understood for having been organized this way. Each title is numbered and used in reference to various rejections in their form paragraphs and/or substantive argument to demonstrate how each aspect applied in distinct manners. After the newly-presented rejections, the response to Applicant's arguments to the Art rejections which were submitted on 6/12/07, are presented.

I. Obviousness Rejections Based on 293 Cells in Serum-Free Mediums

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70-78 and 80-226 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, and Berg, et al. (1993) Biotechniques, 14(6): 972-8.

Note: This is a two-way rejection, applying the Art is slightly distinct manners. The distinct aspects of the first rejection are the use of 293 cells in the media of Perrin, and the distinct aspects of the second rejection are the use of 293 cells in the media of Berg.

With regard to Claims 70-78 and 80-226, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.), particularly serotype 5 adenoviral vectors (e.g., EXAMPLE 2) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (cells comprising an E1A/E1B region) (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Moreover, these compositions are essentially free of BSA, and below the level of a western blot assay, as the compositions are grown in the

absence of BSA (e.g., EXAMPLE 2). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers (e.g., col. 5, lines 1-14), which requires formulation (Id.).

With regard to exogenous coding regions for p53 operatively linked to the CMV-IE promoter (e.g., Claims 85-90), Zhang teaches such (e.g., col. 4, last paragraph).

With regard to vectors missing parts of E1A and/or E1B (e.g., Claims 91-93), Zhang teaches such (col. 4, paragraphs 2-3).

With regard to 293 host cells, which compliment the production of replication incompetent virus (e.g., Claims 94-95), Zhang teaches such (col. 4, paragraph 4)

With regard to the unit doseages and treating a patient with cancer (e.g., Claims 98-100), Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7). Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

Still further, of importance to the arguments to this rejection, is the recognition by Zhang that several methods of infecting (including transfection of DNA by CaPO4 coprecipitation and liposomal transfection) may be used to transform these cells (e.g., EXAMPLE 2).

With regard to all the claims subject to this rejection, Zhang does not explicitly review the general techniques used in the art on how to manufacture the adenoviruses, specifically in importance are those through the steps of growing host cells in a media, providing nutrients to the host cells, infecting the host cells with adenovirus, lysing said host cells, and purifying

adenovirus from the lysate; although Zhang does evidence use of CsCl gradients for purification and formulation (col. 5, paragraph 1). Moreover, the other steps are inherent in Zhang, as these are required steps for growing adenovirus for use. Huyghe evidences these aspects, as Huyghe demonstrates a standard method of making such adenoviruses, in comparison to alternative methods where chromatography substitutes for CsCl centrifugation (TITLE; pp.1407-1408). Specifically, Huyghe teaches that 293 cells are infected with adenovirus vector 2.5 days after growing host cells in media, which provides the nutrients needed to grow, as well as grow adenovirus (p. 1404, col. 1, paragraph 5); cells are lysed to yield adenovirus (Id., last paragraph), and may be purified by cesium chloride (p. 1404, col. 2-1405, col. 1). Moreover, absent to believe otherwise, such produced adenovirus is essentially pure and contains BSA levels below the detection limit of a western blot assay, and is further essentially free of BSA.

With regard to methods that yield substantially pure adenoviral compositions that may be as high as 60-80% , (e.g., Claims 71-72), Huyghe teaches such, which depends on the steps utilized (p. 1408, col. 1, paragraph 2). Hence artisan would be motivated to modify the methods by using different steps and techniques in combination to obtain higher purity.

With regard to the required A260/280 ratios (e.g., Claims 75-77), as has been demonstrated above, the required levels of contaminating nucleic acid are attained in CsCl gradient isolations, and Huyghe teaches that such CsCl gradient purifications yield an AD260/280 of between 1.2-1.3, and reflects variability in the method, which indicates that individual experiments will yield 1.27.

With regard to fed batch processes (e.g., Claim 83), Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5).

With regard to treating the compositions with nucleases and the required levels of contaminating nucleic acid in the compositions (e.g., Claims 73-74, 77, and 96) Huyghe teaches treating the lysate with nuclease (p. 1404, col. 2, paragraph 2), which Applicant demonstrates achieves the required levels of nucleic acid contamination (e.g., TABLE 10).

With regard to BSA levels (All claims, and 70 and 78 in particular), although the Art utilized does not comment on BSA levels in the compositions produced, absent reason to believe otherwise the amount of BSA present is assumed to be under the levels of detection by a western blot assay, and the compositions are assumed to be essentially free of BSA.

However, Zhang does not teach the aspects of serum free media (which also further addresses the levels of BSA as none will be present in serum-free media), bioreactors, microcarriers, and perfusion methods.

On the other hand, Perrin teaches the use of serum-free media, which the Artisan is motivated to use in the manufacture of biopharmaceuticals in order to overcome various problems (p. 1244, col. 2, paragraph 2-p. 1245, col. 1, paragraph 1). Moreover, Applicant teaches that the levels of BSA are caused by the use of serum-free media (e.g., SPECIFICATION, p. 92, paragraph 2). With regard to the use of bioreactors and microcarriers (Claims 80-81), Perrin teaches that it was standard practice in the art to use such bioreactors with microcarriers (p. 1244, col. 2, paragraph 2), as well as the use of perfusion techniques and roller-bottles (Claims 82 and 84) (Id.). Further, of importance to the arguments to this rejection is a demonstration that the Artisan understood that the virus vector could be transformed into the cell by standard viral infection routes (p. 1246, col. 1).

Still further, it was known in the Art that at the time of invention, that the 293 cells of Zhang could be adapted to survive and grow in serum-free media and manufacture biopharmaceuticals (e.g., Berg, et al. (1993) Biotechniques, 14(6): 972-78, ABSTRACT).

Hence, from the confluence of the art provided, the Artisan recognized that there were many methods of growing, providing nutrients, infecting host cells, lysing host cells, purifying adenovirus, and formulating such purified composition to achieve the various required levels of contaminants, etc., as required by the various claims. Hence, the Artisan at the time of invention would have found it obvious to perform the methods using 293 grown in either the serum-free media of Perrin or the serum-free media of Berg.

However, the reader may still question whether or not 293 cells could grow on the serum-free media of Perrin. However, it is noted that Perrin specifically states that several cell types tested were similarly able to grow in the same medium, and no cell line has been reported which will not grow in this medium (e.g., p. 1247, last paragraph). Still further, 293 cells, as shown by Berg, were already known to be able to grow on serum-free media. Moreover, it should be noted that both BHK-21 and 293 cells are kidney cell types. Hence, given the absence of negative teachings, the similarity of cell type, and number of cells adapted to work in this medium, coupled with no finding of any cell type which didn't work and no teaching that other cell types would not work, the Artisan would find it reasonably predicted that 293 cells would grow in this medium.

Hence, at the time of invention by Applicant, the Artisan would have found it obvious to perform the various methods, using the 293 cells of Zhang or Berg, either in the serum-free medium of (i) Perrin or (ii) Berg. The Artisan would have been motivated to do so as both

Zhang and Berg teach several reasons to motivate the Artisan to use serum-free media. Moreover, the Artisan would have had a reasonable expectation of success for such methods as 293 cells had been shown to grow in serum-free media, were well known to grow adenoviral vectors, and to be able to produce recombinant pharmaceutical proteins, which is the same as the cell being transformed by the adenovirus to produce the adenoviral proteins to grow adenovirus.

II. Obviousness Rejections Based on BHK-21 Cells in Serum-Free Media

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70-78 and 80-90, 96-121, 127-152, 158-183, 189-214, and 220-226 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, as further evidenced by Rowe, et al. (1981) J. Virol. 38(1): 191-97.

These rejections are made on the same bases as above, but using the BHK-21 cells of Perrin to grow adenovirus vectors in the serum-free media of Perrin.

The distinct difference here is that the BHK-21 cells are not the 293 cells demonstrated by Zhang to grow adenovirus, and hence, the reader may argue that it was not known if BHK-21

cells could grow adenovirus. However, it was well known in the Art that the adenovirus type 5 of Zhang could be grown in BHK-21 cells at the time of invention. For Example, Rowe teaches that such viruses were known to grow in BHK-21 cells (e.g., ABSTRACT), and hence, the Artisan knew that these cells supported the growth of adenovirus serotype 5.

Still further, with regard to the various distinctions in the claims for various requirements of steps and results, the Examiner relies on the same basis as previous rejections. Essentially, these techniques were all already known in the Art for growing, lysing, and purifying cells, and the Artisan would therefore be motivated to use any particular combination of them, depending on the desired results.

Hence, at the time of invention by Applicant, the Artisan would have been motivated to use perform the various methods claimed, utilizing Ad5 cells grown in the BHK-21 cells of Perrin within the serum-free medium of Perrin. The Artisan would have been motivated to do so in order to produce virus in absence of serum, as taught by Perrin. Moreover, the Artisan would have had a reasonable expectation of success, as Perrin had taught BHK-21 cells could grow in serum free media, and further grow virus in such media, and Rowe evidenced that the Artisan already knew that BHK-21 cells supported growth of an adenovirus of Rowe.

III. Obviousness Rejections Based on Culture Systems with Horse Serum

Claims 101-109, 111-140, 142-171, 173-202, and 204-226 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human

Gene Therapy, 6: 1403-1416, and as evidenced by Perrin, et al. (1995) Vaccine, 13(13): 1244-50 as applied to the various aspects not requiring the serum-free media of obviousness rejections of Title I, above.

The subject claims are also rejected under the same bases as Title I., above, however, not utilizing the serum-free medium or cells of Perrin, but only relying on Perrin for the other aspects of the rejection, e.g., bioreactors, microcarriers, and roller bottles.

It is noted that Zhang teaches growing the adenovirus in cells on horse-serum supplemented medium, and hence, absent reason to believe otherwise, this medium contains no BSA (bovine serum albumin). Hence, absent to believe otherwise, the obtained virus particles would not contain BSA, and would necessarily be below the level of a western blot assay.

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Zhang with the steps of culturing, feeding, etc., of Perrin, to grow the cells in 293 cells in horse-serum supplemented medium. The Artisan would have been motivated to do so because such methods were known and standard in the Art, and absent reason to believe otherwise, the derived compositions would be BSA free. Moreover, the Artisan would have had a reasonable expectation of success as the virus had already been grown in the absence of BSA, and Perrin's techniques were well known in the art.

IV. Further Obviousness Rejections Based on NA Levels Below 0.2ng/mL

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 74, 105, 136, 167, and 198 are newly further rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002, as further evidenced by Huyghe, et al. (1995) Human Gene Therapy, 6: 1403-1416, and further in view of Perrin, et al. (1995) Vaccine, 13(13): 1244-50, and optionally Berg, et al. (1993) Biotechniques, 14(6): 972-79, and optionally evidenced by Rowe, et al. (1994) J. Virology, 38(1): 191-97, as applied to claims 70, 101, 132, 163, and 194, respectively above, and as further evidenced by Nadeau, et al. (1996) Biotechnology and Bioengineering, 51: 613-623, or Trepanier, et al. (1981) J. Virological Methods, 3: 201-11

As is shown above, Zhang as evidenced by Huyghe and Perrin and optionally Berg, as optionally evidenced by Rowe make obvious the various aspects of claims 70, 101, 132, 163, and 194 in several manners, as shown in Titles I-III, above; however, they do not specifically discuss obtaining nucleic acid contaminations less than 0.2ng/mL, and hence, the reader may argue that the Artisan would not have expected to obtain such levels of contamination.

On the other hand, the other two references (Nadeau and Trepanier) each teach the use of ultrafiltration in the purification of viral particles (e.g., Nadeau, p. 615, col. 1, paragraph 1). As such, these steps are generally known in the art for purification. Moreover, Applicant's

specification makes clear that such ultrafiltration step yields the desired levels of contaminating nucleic acids (SPECIFICATION, TABLE 10). Hence, such ultrafiltration step would necessarily yield the desired levels of contaminating nucleic acid.

At the time of invention by Applicant it would have been obvious to modify the methods of Titles I-III, above, by the ultrafiltration step of either Nadeau or Trepanier. One would have been motivated to do so because such steps are known in the art for concentration and purifying adenovirus. Moreover, the Artisan would have had a reasonable expectation of success, as these methods were already known successful.

Response to Argument Rebutting Art Rejections

Applicant's argument of 6/12/07 has been fully considered, but is not found persuasive, or the rejections have been reapplied to overcome the arguments.

Applicant argues that all the rejections rely on Perrin for the express teaching of serum-free media to grow virus (p. 24, paragraph 4).

Such is not persuasive. Several rejections were applied to the claims in the Official Action of 8/8/06 which did not require the teaching of serum-free media of Perrin, however, such rejections have been withdrawn, and in order to remove such confusion in the future, the rejections are now reapplied, clearly explaining such differences. Applicant is directed, for example, to those rejections under Title III, above.

Applicant argues that Perrin states that the serum affected the BHK-21 cells by "modifying their sensitivity to rabies virus or had selected apparently less sensitive cells.", citing page 1249, col. 1, first paragraph. Using this, Applicant argues that the serum had an adverse

affect on the BHK-21 cells, resulting in a loss of sensitivity to rabies virus infection, then argues "Who knows what [the effects would be for adenovirus]?" They then argue that this represents a high degree of uncertainty as to whether adenovirus would even grow in either BHK-21 or 293 cells (p. 25, paragraph 2).

Such is not persuasive. The finding at no point indicates that the cells were not quite as efficient at first for being transfected by Rabies virus, but then, over a few passages, became very susceptible to rabies virus transfection. However, at no point are the cells unable to be infected by Rabies virus. Still further, with regard to infecting the cells, the adenovirus may be transfected into cells via CaPO4 methods, liposomal methods, or even the normal route of infection, and hence, sensitivity to being infected virus would be overcome by the non-viral routes of infection. This information is provided in the rejections above, in order to support the Examiner's arguments. Moreover, the sensitivity problems were also apparently easily overcome by minor modifications known in the Art (pp. 1248-49, paragraph bridging). Hence, such passage appears to be more of an extrapolation to gargantuan proportions from a minor observation provided by Perrin, which is easily overcome by the Artisan adjusting parameters. This is further supported by the fact that Perrin does not even state that this means that other cells or viruses may be completely blocked from infecting such cells.

Applicant argues that the Examiner has not provided information in the prior Art that 293 cells could even be grown in serum-free conditions (p. 25, paragraph 3).

Such is not persuasive. As shown above, it was known in the Art that 293 cells could grow in serum-free conditions, and even produce transgenic proteins, as is required to make the adenovirus. Still further, several rejections do not even require 293 cells, and/or serum-free

conditions, and as such, these rejection can be rejected under other bases (e.g:, Titles II-IV, above).

Applicant argues that Perrin's statement that serum-free media has not been used for the production of classical viral vaccines, argues that there is no motivation or reasonable expectation of success to use Perrin's method for growing adenovirus (p. 25, last paragraph-p. 26, paragraph 2).

Such is not persuasive. First, Perrin does make such a statement, but then goes on to show a just such a method. Second, Perrin shows that viruses may be grown in such media, and simply demonstrates that they were the first to demonstrate the novel method. Further, to argue that the Artisan would not be motivated to look to Perrin is not considered persuasive, given the recent court decision *KSR International Co. v. Teleflex Inc.,* 550 US --, 82 USPQ.2d 1385 (2007), as well as the fact that Perrin provides ample motivation (e.g., p. 1244, col. 2, paragraph 2). With regard to a reasonable expectation of success, Perrin shows that his serum-free media can grow virus, and thus, it can produce the proteins transgenically required to do so, and so the Artisan would have a reasonable expectation that such could be performed a distinct virus. Still further, 293 cells were known to grow in serum-free media, similarly producing transgenic proteins, and BHK-21 cells were also known to grow adenovirus type 5. Hence, there is a reasonable expectation of success. The Examiner simply has no specific argument, supported by logic to demonstrate why these cells would not grow in the media, or that either cell would not produce viral particles.

Applicant argues that the references used, other than Perrin do not teach or suggest the use of serum-free media (p. 26, paragraph 3).

Such is not persuasive. The other references are not used in anticipation rejections, but in obviousness rejections, and are not required to each teach the serum-free media limitation. Moreover, the newly-supplied reference: Berg, teaches 293 cells growing on serum-free media. Furthermore, several claims do not require serum free, and hence, several rejections are based on other aspects from Perrin, but not the use of serum-free media.

Applicant argues that Perrin teaches an enveloped virus (one that utilizes the cell membrane of the cell in which it grows to bud off, and therefore being enveloped in a modified cell membrane), while adenovirus is a DNA capsid virus (one that simply is encapsulated in transgenically-made protein envelope), and hence, due to the distinct method of encapsulation, the Artisan would not have predicted success in the system for such an adenovirus (p. 26, paragraph 4).

Such is not persuasive. Perrin's rabies virus and the adenovirus both require proteins to be made transgenically from the viral genome. In the case of the rabies virus, the only distinct protein mechanism in encapsulation is the trafficking of some viral proteins to the cell envelope, and Perrin demonstrates that this works, but in doing so, it also demonstrates that proteins can be made transgenically. Hence, the transgenic proteins made to make the viral envelope of the adenovirus would be reasonably predicted to be produced, and hence, allow encapsulation of the adenovirus.

Applicant broadly avers that the distinct biological replication cycles of the adenovirus and the rabies virus makes it such that the Artisan would not provide a reasonable expectation of success for the use of Perrin (pp. 26-27, paragraph bridging).

Such is not persuasive. Broad aversion does not supplant the need for specific argument, evidence, or demonstration of a failure in logic provided by the Examiner's rejections. Hence, for the reasons provided above, there is a reasonable expectation of success.

Applicant argues, citing a declaration originally provided in the prosecution of Application No. 09/203,078, that because rabies virus is RNA based, and adenovirus is DNA based that there is no reasonable expectation of success for producing adenovirus based on the showing by Perrin of the growth of an RNA virus (p. 27, paragraph 2).

Such is not persuasive. The argument that rabies virus is an RNA based virus, and does not require DNA replication to obtain viral genome for replication is misleading. In fact, the adenovirus is distinct in this manner in that the genomic DNA is replicated rather than RNA being made from RNA, but such mechanisms utilize the normal aspects provided by living replicating cell, DNA replication mechanisms. Moreover, the proteins that are distinct from those provided by the cell are provided by the adenovirus transgenically, which has already been shown successful for these cells. Still further, because the cells are alive, those proteins provided by the cells for replication are necessarily present, otherwise the cell would not replicate its own DNA and grow.

Applicant argues that the Examiner's rejection, stating that the methods of Perrin were standard in the Art is incorrect for the use of serum-free media, and such are not standard in the Art (p. 27, paragraphs 2-4).

Such is not persuasive. The Examiner had stated that the other methods of Perrin relied upon (e.g., roller bottles) were standard in the Art. However, for clarity, the rejections have been rewritten and clarified above.

Applicant argues that the Examiner uses hindsight to reject the claims for the use of serum-free media (Id.).

Such is not persuasive. Every rejection is necessarily made on hindsight, as the Examiner must match the various aspects of the claims. However, on the basis of serum-free media, the motivation provided is found in Perrin and Berg, not in Applicant's disclosure, although it is apparent that Applicant's disclosure provides much the same motivation. To argue that the Examiner cannot use a motivation in the Art because it is also provided by Applicant's disclosure is simply incorrect.

Applicant argues the Examiner's statements that Perrin provides an art-accepted methodology to remove contaminants such as BSA is not of issue, but simply whether or not it could be accomplished (p. 28, paragraphs 1-2).

Such is persuasive. The Examiner hopes that the rejections as rewritten make this issue clear. To wit, the methodology is accepted to remove BSA, and the argument is whether or not the Artisan would have had a reasonable expectation of success.

Applicant argues that Perrin is not applicable to the other art used in the rejections but only relates to Rabies virus production, and that the distinct biological cycles of adenovirus and rabies virus would preclude a motivation to combine references (p. 28, paragraph 3).

Such is not persuasive. Perrin relates to producing viruses in serum-free media. Perrin also, as shown above, provides reasons to produce viruses in serum-free media. Hence, there is ample reason to combine these references. Moreover, to argue that because one virus replicates in a distinct manner means that the Artisan would not look to the other virus's art is simply incorrect. The Artisan is one with expertise in virology. To say that they would not look in

another portion of the Art to find the reference, and be able to apply it to a new virus is simply not correct. Applicant is advised to read *KSR International Co. v. Teleflex Inc.*, 550 US --, 82 USPQ.2d 1385 (2007). Still further, several references do not rely upon Perrin's teaching of serum-free media, but simply the other teachings on culturing cells and viruses, and as such those rejections would still apply regardless of the argument.

Applicant rehashes the arguments for the sensitivity to rabies virus infection (pp. 28-29, paragraph bridging).

Such is not persuasive. The same argument as above is given: The finding at no point indicates that the cells were not quite as efficient at first for being transfected by Rabies virus, but then, over a few passages, became very susceptible to rabies virus transfection. However, at no point are the cells unable to be infected by Rabies virus. Still further, with regard to infecting the cells, the adenovirus may be transfected into cells via CaPO4 methods, liposomal methods, or even the normal route of infection, and hence, sensitivity to being infected virus would be overcome by the non-viral routes of infection. This information is provided in the rejections above, in order to support the Examiner's arguments. Moreover, the sensitivity problems were also apparently easily overcome by minor modifications known in the Art (pp. 1248-49, paragraph bridging). Hence, such passage appears to be more of an extrapolation to gargantuan proportions from a minor observation provided by Perrin, which is easily overcome by the Artisan adjusting parameters. This is further supported by the fact that Perrin does not even state that this means that other cells or viruses may be completely blocked from infecting such cells.

Applicant again argues that Perrin teaches away from growing adenoviruses in serum free media. Applicant argues that Perrin's statement that serum-free media has not been used for the

production of classical viral vaccines, argues that there is no motivation or reasonable expectation of success to use Perrin's method for growing adenovirus (p. 29, paragraphs 3-5).

Such is not persuasive. First, Perrin does make such a statement, but then goes on to show a just such a method. Second, Perrin shows that viruses may be grown in such media, and simply demonstrates that they were the first to demonstrate the novel method. Further, to argue that the Artisan would not be motivated to look to Perrin is not considered persuasive, given the recent court decision *KSR International Co. v. Teleflex Inc.,* 550 US --, 82 USPQ.2d 1385 (2007), as well as the fact that Perrin provides ample motivation (e.g., p. 1244, col. 2, paragraph 2). With regard to a reasonable expectation of success, Perrin shows that his serum-free media can grow virus, and thus, it can produce the proteins transgenically required to do so, and so the Artisan would have a reasonable expectation that such could be performed a distinct virus. Still further, 293 cells were known to grow in serum-free media, similarly producing transgenic proteins, and BHK-21 cells were also known to grow adenovirus type 5. Hence, there is a reasonable expectation of success. The Examiner simply has no specific argument, supported by logic to demonstrate why these cells would not grow in the media, or that either cell would not produce viral particles.

Applicant argues that there is no expectation for compositions free of BSA or below the level of a western blot assay (p. 29, paragraph 3).

Such is not persuasive. If the virus is grown in the BSA, it must be free of BSA. Such is a purpose of growing the virus in serum-free media as in Perrin, and further shown in Berg. Further, for those references not requiring Perrin's teaching of serum-free cultures, Zhang utilizes horse serum. Necessarily, such serum does not contain bovine serum albumin. The

Examiner has no reason to believe such compositions would contain bovine serum albumin. In addition, the office cannot perform experiments, so it is left to applicant to demonstrate otherwise.

Applicant argues that the withdrawal of rejections not using Perrin demonstrate that the references do not teach or suggest the use of serum-free media, and further that Perrin is limited to rabies virus, which is distinct from adenovirus in its replication cycle, and as such the Artisan would have predicted that the method would be successful.

Such is not persuasive. As shown above, there is no reason to believe the method would not work, and further, Applicant's arguments do not appear to address an aspect of a difference between the cycles of each virus such that the Artisan would not reasonably predict such method to work.

Applicant rehashes the argument that the life-cycles are distinct between rabies and adenoviruses, such that there is no reasonable expectation of success (pp. 30-31, paragraph bridging).

Such is not persuasive for the reasons provided above: e.g., Perrin's rabies virus and the adenovirus both require proteins to be made transgenically from the viral genome. In the case of the rabies virus, the only distinct protein mechanism in encapsulation is the trafficking of some viral proteins to the cell envelope, and Perrin demonstrates that this works, but in doing so, it also demonstrates that proteins can be made transgenically. Hence, the transgenic proteins made to make the viral envelope of the adenovirus would be reasonably predicted to be produced, and hence, allow encapsulation of the adenovirus. Still also, with regard to DNA replication, the argument that rabies virus is an RNA based virus, and does not require DNA replication to

obtain viral genome for replication is misleading. In fact, the adenovirus is distinct in this manner in that the genomic DNA is replicated rather than RNA being made from RNA, but such mechanisms utilize the normal aspects provided by living replicating cell, DNA replication mechanisms. Moreover, the proteins that are distinct from those provided by the cell are provided by the adenovirus transgenically, which has already been shown successful for these cells. Still further, because the cells are alive, those proteins provided by the cells for replication are necessarily present, otherwise the cell would not replicate its own DNA and grow

Applicant again argues that serum-free methods were not standard in the art (p. 31, paragraphs 2-3).

As stated above, the Examiner has modified the rejections to demonstrate that the serum-free methods are distinct from those other methods demonstrated by Perrin, e.g., roller bottles.

Applicant again argues hindsight (p. 31, paragraph 3).

Such is not persuasive. As stated above, rejections are necessarily to some extent made on hindsight, as the claimed limitations must be taught. However, the various aspects and motivation, although also provided in Applicant's specification, are also present in the Art used. Hence, because the Examiner was not required to cite Applicant's specification for the rejection, there is no use of Applicant's disclosure to formulate the rejection. Simply because Applicant discloses something does not preclude the Examiner from using the same knowledge if it is present in the prior art.

Applicant again argues that the issue of desire to remove BSA is not at issue, and instead the issue is one of reasonable predictability (p. 31, last paragraph).

Such is persuasive. The Examiner hopes that the rejections as rewritten make this issue clear. To wit, the methodology is accepted to remove BSA, and the argument is whether or not the Artisan would have had a reasonable expectation of success.

Applicant argues that the majority of references do not teach the roller-bottles, perfusion techniques, etc., but only teach other aspects not taught by Perrin, and there is therefore no reason to combine these teachings with those of Perrin (pp. 32-33, paragraph bridging).

Applicant argues that the rejections only using Perrin for teachings of, e.g., bioreactors and microcarriers, but not for serum-free culture conditions should be withdrawn, because Perrin does not say to combine these methods with the various other methods (p. 32, paragraph 4-5). There are also other arguments that the other references do not teach the various aspects for use in adenovirus art (p. 33, paragraphs 2-3)

Such is not persuasive. The teachings demonstrate that these are standard methods known to the Artisan when designing a method to culture cells and grow virus. To say that the Artisan would not have been able to apply them to other methods is simply incorrect. Still further, to argue that these methods are not standard culture techniques is simply incorrect. The Artisan would have been well aware of them to the point that these techniques were known in standard manuals for laboratory techniques, e.g., stirred bioreactors are cited in the table of contents provided by Applicant from "Animal Cell Culture, A Practical Approach", Edited by RI. Freshney (1992), by Oxford University Press, Oxford, Great Britain, page x. Still further, the Artisan would have been aware of Perrin, and it was not beyond the capability of the Artisan to Apply these methods in other systems of cell culture/viral propagation. Applicant is advised to read *KSR International Co. v. Teleflex Inc.*, 550 US --, 82 USPQ.2d 1385 (2007).

Applicant argues that rejections to Claims 82, 113, 144, 175 and 206 should be withdrawn, as Applicant has shown an unexpected result: a cleaner and more high purified adenovirus composition (p. 33, paragraph 4, citing the specification, p. 11, line 23-p. 12, line 10).

Such is not persuasive. Applicant's finding is not commensurate with what is claimed, specifically, the reported result cited in the specification is the use of the Cellcube™ bioreactor with perfusion rates that are "low to medium". As such, the claims are actually broader than the cited paragraph, and are still properly rejected.

Applicant argues that the specification demonstrates that the rejections of Claims 101-226 are improper as it demonstrates improvements in yield (p. 34, paragraph 1).

Such is not persuasive. In each case of an improved yield specific method steps, utilizing specific culture techniques, lysing techniques, purification techniques, and formulation techniques arrive at the various aspects, however, no claim encompasses any specific combination of techniques which provides any unexpected result. Moreover, the Art demonstrates in most instances that the required levels of any particular contaminant are obtained, and also provides reasoning to use any particular technique. As such, the rejections are still proper, as no claim is even commensurate with any particular unexpected result.

Applicant argues that Huyghe discloses CsCl, with only 23% virus recovery, and the method of the invention provides purities down to 60gp/mL and one embodiment achieving 70+/-10% virus recovery (p. 34, paragraph 2).

Such is not persuasive. As shown above, Hugh recognizes that, depending on the steps utilized, the various levels of recovery can be obtained, and his particular experiment demonstrates an example. With regard to 60pg/mL purity, such is not claimed, and hence, not

considered. With regard to 70+/-10% recovery, as well as the purities, it is well within the ability of the Artisan to optimize yields and utilize the various steps to yield higher recoveries. With the explicit teaching in Huyghe, it is clear that the Artisan would find it obvious to utilize and optimize these methods to obtain the recovery characteristics desired. Applicant is advised to read *KSR International Co. v. Teleflex Inc.,* 550 US --, 82 USPQ.2d 1385 (2007).

Applicant argues that the rejection of Claim 167 should be withdrawn on the basis that it only optionally requires Perrin (p. 34, paragraph 3).

Such is persuasive. The Examiner apologizes for not making the rejections more clear. The simple problem is that with 156 claims to reject in complex in permutations, it is difficult to organize the rejections in such a manner that they are clear. However, the Examiner hopes it is done correctly and clearly in this set of rejections.

Applicant argues that Huyghe teaches only 23% viral recovery, and Applicant demonstrates that their method provides higher purity than CsCl gradient techniques, with higher throughput, and therefore, Huyghe cannot be used to demonstrate 70+/-10% recovery, and hence, the Examiner has not demonstrated that there is a reasonable expectation of success for such purity and levels of contamination, as in Claim 167.

Such is not persuasive. Huyghe demonstrates that, depending on the steps chosen, higher recoveries can be obtained (ABOVE). Hence, it is clear that the Artisan would be motivated to modify the methods to obtain higher yields and purity. Moreover, given that there are not an infinite number of permutations, it is also clear that the Artisan could find the method steps required to obtain such a yield. Applicant is advised to read *KSR International Co. v. Teleflex Inc.,* 550 US --, 82 USPQ.2d 1385 (2007).

Applicant argues that Nadeau, while teaching ultrafiltration, it teaches such for the purification of virus from supernatant, and hence, the Artisan would not perform it for removal of contaminants from adenoviral compositions (p. 35, paragraph 2).

Such is not persuasive. In teaching the removal of adenovirus from a solution, the Artisan instantly recognizes the use of such to obtain the adenovirus, as much as to obtain the supernatant. Applicant is advised to read *KSR International Co. v. Teleflex Inc.*, 550 US --, 82 USPQ.2d 1385 (2007).

Applicant argues that because Trepanier is directed to ultrafiltration with HSRV, the Artisan would not apply Trepanier to adenovirus, due to size differences (p. 35, paragraph 3).

Such is not persuasive. The Artisan would instantly recognize to use this method for any separation of viruses, and simple adjustment of filter size is considered well within the skill of the Artisan. Applicant is advised to read *KSR International Co. v. Teleflex Inc.*, 550 US --, 82 USPQ.2d 1385 (2007).

Applicant argues that it is hindsight teaching to use either Nadeau or Trepanier and does not establish that the Artisan would have been motivated to do so before the filing of Applicant (p. 35, last paragraph).

Such is not persuasive. Both Nadeau and Trepanier teach the use of ultrafiltration in the separation of viruses from contaminants. The Artisan would have known how to apply this to purify adenoviruses. Moreover, the Artisan would have been motivated to do so because, as shown above, these are standard methods known in the art. The Artisan would have been motivated to use to make their methods more efficient.

Applicant argues that there is no teaching in the Art that 0.2 ng/mL or 0.8ng/mL could be obtained for levels of nucleic acid contamination, and as such, the Artisan would not have expected success in such method (p. 36, paragraph 1).

Such is not persuasive. There is no negative teaching in the Art, and the Artisan was motivated to obtain more efficient methods to obtain their compositions with higher purity. Hence, the Artisan would have been motivated to find those methods, and further would have had a reasonable expectation of success. Applicant is advised to read *KSR International Co. v. Teleflex Inc.*, 550 US --, 82 USPQ.2d 1385 (2007).

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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